NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA267; Ivabradine for the treatment of chronic heart failure

Original publication date:	November 2012
Review date	November 2015
Existing recommendations:	Optimised To see the complete existing recommendations and the original remit for TA267, see Appendix A.

1. Proposal

The TA267 guidance should be incorporated into the on-going update of NICE clinical guideline 108 and transferred to the static list. That we consult on this proposal.

2. Rationale

NICE clinical guideline 108 (Chronic heart failure in adults: management) is currently being updated, with an anticipated publication date of August 2018. Evidence has been identified that suggests ivabradine may be clinically effective for people with less-impaired left-ventricular ejection fraction, which may allow the recommendation in TA267 to be broadened. However, the number of people affected by this approach is unknown, so the value of a technology appraisal review may be limited. Therefore, it is proposed that the:

- left ventricular ejection fraction caveat of the recommendation be reviewed in the update of CG108, if considered appropriate by the guideline development team.
- existing recommendations in TA267 guidance are transferred to the static list (maintaining the funding direction) because the identified evidence since its initial publication does not suggest that a review of TA267 is necessary.

3. Summary of new evidence and implications for review

The updated literature searches identified a number of new publications, including clinical trials, systematic reviews and meta-analyses.

Several publications report analyses of the SHIFT trial, the key trial considered in TA267 (for example, Bocchi et al. 2015; Bohm et al. 2010; Borer et al. 2012; Borer et

al. 2014; Borer et al. 2017; Krum and Sindone 2013; Swedberg et al. 2010; Tavazzi et al. 2013). In addition, new studies (INTENSIFY; Zugck et al. 2014 and RELiF-CHF; Zugck et al. 2017) and meta-analyses (Burnett et al. 2014; Deschaseaux et al. 2014; Thomsen et al. 2016) support the clinical effectiveness of ivabradine for treating chronic heart failure. These publications provide evidence consistent with the recommendations in TA267.

Evidence addressing uncertainties in TA267 provides further support for the existing recommendations. In particular, the Committee highlighted uncertainty in the effectiveness of ivabradine with increasing beta-blocker doses, and more recent studies (for example, Al Saadi et al. 2013; Bagriy et al. 2015; Bocchi et al. 2015; Hidalgo Lesmes et al. 2016; Swedberg et al. 2012; Volterrani et al. 2011) appear to support the effectiveness of ivabradine in combination with beta-blockers. In addition, the Committee considered that the benefit of ivabradine in people with more severe heart failure was uncertain, although the recommendations were not restricted to particular classes of heart failure. A post hoc analysis of the SHIFT trial suggests that the effectiveness of ivabradine in severe heart failure (New York Heart Association class IV and left-ventricular ejection fraction 20% or less) is similar to those with less severe disease (New York Heart Association classes II or III and left-ventricular ejection fraction more than 20%; Borer et al. 2014). Zugck et al. (2015) reports that the effect of ivabradine was more pronounced in people with more severe heart failure. These studies do not suggest that a review of the recommendations in TA267 is needed.

Conversely, some evidence has been identified that suggests a reduced benefit or increased risks associated with ivabradine. Chaudhary and Rawat (2014) report a study of 1500 people with heart failure for whom beta-blockers were contraindicated, and found no statistically significant difference between ivabradine and placebo in mortality, morbidity or hospitalisation rates. However, this study is substantially smaller than the SHIFT trial. In addition, a meta-analysis (Martin et al. 2014) suggested that the risk of atrial fibrillation associated with ivabradine may be higher than reported in the Summary of Product Characteristics. These studies suggest that reconsideration of the recommendations may be warranted, particularly for people for whom beta-blockers are contraindicated; however, it is unclear whether either study would provide sufficient evidence to revise the recommendations.

The recommendations in TA267 were restricted to people with a left-ventricular ejection fraction of 35% or less, consistent with the entry criteria for the SHIFT study. However, an ejection fraction level is not specified in the marketing authorisation for ivabradine. Several publications have been identified which report the clinical effectiveness of ivabradine in populations with less-impaired ejection fractions (less than 40% or less than 50%; for example, Gurcagan and Altay 2015; Hamayak et al. 2014; Hidalgo Lesmes et al. 2016; Lofrano-Alves et al. 2015; Mansour et al. 2011; Narayanan et al. 2017; Peck et al. 2014; Riccioni et al. 2013). The evidence suggests that ivabradine is clinically effective in these groups, although most are relatively small studies. If ivabradine was clinically effective in people with a left-ventricular ejection fraction greater than 35%, it may be possible to broaden the recommendation in TA267. However, the number of people that would be affected by such a change is unknown, and therefore a technology appraisal may be of limited value. It may be more appropriate to review the additional evidence for

ivabradine in people with less-impaired left-ventricular ejection fractions within the ongoing update of NICE clinical guideline 108.

Since publication of TA267, technology appraisal 314 has been published, recommending implantable cardioverter defibrillators and cardiac resynchronisation therapy as options for some people with heart failure, and some new evidence for the relative effectiveness of cardiac devices and ivabradine has been identified (Peck et al. 2014). However, the relative positions of ivabradine and cardiac devices in the treatment pathway for heart failure are uncertain: in TA267, the Committee noted that there are some people for whom either ivabradine or a cardiac device may be suitable (and the choice is likely to be made on clinical judgment), but TA314 states that cardiac devices are indicated for people who have heart failure symptoms despite optimal pharmacological therapy. The relative effectiveness and position in the treatment pathway of ivabradine and cardiac devices would be most appropriate to consider in the context of a clinical guideline update.

In addition, technology appraisal 388 published in 2016, recommends sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction, in people with New York Heart Association class II to IV symptoms, a left ventricular ejection fraction of 35% or less and who are already taking a stable dose of angiotensin‑converting enzyme inhibitors or angiotensin II receptor‑blockers. Sacubitril valsartan is recommended before ivabradine in the treatment pathway and therefore does not affect the recommendations in TA267.

Has there been any change to the price of the technology(ies) since the guidance was published?
No.
Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?
The company has confirmed that there are no existing or proposed changes to the marketing authorisation that would affect the existing guidance.
Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?
Please see summary above.
Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?
See Appendix C for a list of related NICE guidance. CG108 (Chronic heart failure in adults: management) is being updated, with an expected publication date of August 2018. The recommendations from TA267 can be incorporated into the new clinical guideline.
Additional comments

The search strategy from the original manufacturer report for ERG was adapted and re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from January 2012 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section above. See Appendix C for further details of ongoing and unpublished studies.

4. Equality issues

In TA267, the Committee considered that there were no equality issues that affected its recommendations. It concluded that the recommendations did not have a particular impact on any of the groups whose interests are protected by the legislation and that there was no need to alter or add to the recommendations.

GE paper sign off: **Meindert Boysen,** 14 December 2017

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Appendix A – Information from existing guidance

5. Original remit

To appraise the clinical and cost effectiveness of ivabradine within its licensed indication for the treatment of chronic heart failure.

6. Current guidance

1.1 Ivabradine is recommended as an option for treating chronic heart failure for people:

- with New York Heart Association (NYHA) class II to IV stable chronic heart failure with systolic dysfunction and
- who are in sinus rhythm with a heart rate of 75 beats per minute (bpm) or more and
- who are given ivabradine in combination with standard therapy including beta-blocker therapy, angiotensin-converting enzyme (ACE) inhibitors and aldosterone antagonists, or when beta-blocker therapy is contraindicated or not tolerated and
- with a left ventricular ejection fraction of 35% or less.

1.2 Ivabradine should only be initiated after a stabilisation period of 4 weeks on optimised standard therapy with ACE inhibitors, beta-blockers and aldosterone antagonists.

1.3 Ivabradine should be initiated by a heart failure specialist with access to a multidisciplinary heart failure team. Dose titration and monitoring should be carried out by a heart failure specialist, or in primary care by either a GP with a special interest in heart failure or a heart failure specialist nurse.

7. Research recommendations from original guidance

None.

8. Cost information from original guidance

“Ivabradine is available in 5 mg and 7.5 mg tablets at a net price of £40.17 per 56-tablet pack (excluding VAT; 'British national formulary' [BNF] edition 63). The manufacturer's submission quoted an average monthly cost of £42.10 (excluding VAT) based on the proportion of patients using 2.5 mg (7%) and either 5 mg or 7.5 mg (93%) in the SHIFT study (see section 3.1).”

Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the specify STA or MTA process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to specify date or trial.	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	Yes

Appendix B

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline[1].	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	No
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Appendix C – other relevant information

Relevant Institute work

Published

Chronic heart failure in adults: management (2010) NICE guideline CG108. *An update is in development, the expected publication date is August 2018.*

Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction (2016) NICE technology appraisal guidance 388

Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure (2014) NICE technology appraisal guidance 314

Appendix D – References

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